Physiology of the Aging Kidney
We Know Where We Are Going, but We Don't Know How …

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Senescence could be defined as the gradual deterioration of functional characteristics in living organisms. The word senescence can refer to either cellular senescence or to senescence of the whole organism. Kidney senescence has been well described at the cellular and microscopic levels, with a distinction between the microstructural changes observed in normal physiologic aging versus in diseases (1,2). The effect of kidney senescence on GFR has been relatively well described but mainly from cross-sectional data, which are not ideal from a methodologic point of view (1,3–5). After a period of kidney maturation in the first years of life, GFR remains constant until around 40 years. From the fourth decade, GFR is declining in line with the loss of nephrons (1). However, several important questions are still open. Is this decline observed in everyone? Is this physiologic decrease in GFR the same in men and women? Is this decline in GFR linear? Also, the evolution of GFR at the extremes of life is, by nature, difficult to study. Recently, Smeets *et al.* (6) assembled cross-sectional data from the literature to describe the evolution of GFR during the first 5 days after birth. On the other side of the age curve, data on GFR evolution in the elderly are scarce. Ideally, GFR slopes should be studied with longitudinal data using the measured GFR (exogenous clearance methods), but this is very challenging.

In this issue of *CJASN*, Schaeffner *et al.* (7) studied the course of GFR with age in a longitudinal study of 2069 community-dwelling older persons (mean age of 80±7 years old; the Berlin Initiative Study [BIS]) with eGFR and a follow-up time of 6.1 years. Study participants were members of the largest German statutory health insurance living in Berlin. The response rate in the BIS cohort has been reported to be relatively low (8%), but the loss to follow-up and the number of missing data were low in this study. The goal of the authors was double: "describe the crude and adjusted age-related course of eGFR in a population of individuals aged ≥70" and "define reference values for both sexes" (7). In our opinion, the population studied does not allow the authors to really "define" reference values. Indeed, although large and population based, their population may not be representative of the global German population over 70 years (and the authors never claimed such representativeness). Also, their population is obviously not a healthy one (*e.g.*, 26% with diabetes, 79% with hypertension, and 29% with heart failure), and therefore, *sensu stricto*, the term "reference values" is probably not applicable to the results. Having said that, the authors add arguments to those from several authors who have criticized the unique, fixed GFR threshold at 60 ml/min per 1.73 m^2, still considered for the diagnosis of CKD. The current CKD definition, not adapted to age, overestimates the CKD prevalence in the elderly population (and underestimates the prevalence in young people) (5). Indeed, with this fixed threshold, after 75 years, half of the cohort should be labeled as CKD.

The second objective of the authors was to study the course of eGFR with aging. They concluded that when eGFR was estimated by an equation on the basis of cystatin C, the decline in GFR was not linear. The 1-year slope was less steep in the oldest (at 90 years) participants than in the youngest (at 70 years). The first evident explanation would be that this is due to a survival bias, with healthier participants (the survivors) having a lower decline in eGFR with aging, but the authors convincingly showed that this hypothesis did not explain the nonlinear decline rate. However, it must be underlined that this nonlinearity in the GFR course with aging is only observed with cystatin C–based equations. In other words, using the Chronic Kidney Disease Epidemiology (CKD-EPI) or the European Kidney Function Consortium (EKFC) creatinine-based equations, the 1-year slopes were not different in the different age ranges. The age-related decline in eGFR proposed by Schaeffner *et al.* (7) is inherent to their own cohort, and further analyses in other cohorts would be of interest. As acknowledged by the authors, the interpretation of their results on slopes is not easy. First, in their statistical analyses, they did not include any term for individual slopes; thus, the results should be interpreted as a combination of cross-sectional GFR-age associations and longitudinal changes in GFR. Second, as mentioned, the population is not healthy, and part of the GFR decline could be due to residual confounding from disease or risk factors. Moreover, adjustment is made on baseline characteristics, but changes in risk factors and treatment of, for example, hypertension and diabetes during aging and follow-up could influence the change in GFR. The authors did not consider the medications of the participants, arguing that "they were considered

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parts of the causal pathways," but some medications, like angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or sodium-glucose cotransporter 2 inhibitors, may strongly affect the eGFR slope. Third, the discrepancy observed between creatinine and cystatin C equations deserves some comments. Here, the construction of the estimating equations should be considered. These equations have been mathematically constructed to estimate GFR in a cross-sectional design (for a given person at a given time). The measured GFR is found to be constant until 40 years and then decreases, whereas both serum creatinine and cystatin concentrations have been found to be relatively constant until the fifth decade (8). The association between serum creatinine, cystatin C, and GFR is thus changing with aging. For this reason, age is a variable in all eGFR equations: $age^{-0.57}$ in the $BIS2_{creatinine+cystatin\ C}$, 0.9938^{age} in the $CKD\text{-}EPI_{creat}$, 0.9961^{age} in the $CKD\text{-}EPI_{cystatin}$, and $0.990^{(Age\ -\ 40)}$ in the EKFC study. The effect of the mathematical form applied to age in all of these equations (but also, the effect of the baseline eGFR) on the interpretation of the eGFR slopes in the elderly is particularly challenging. Another example is the large bias of the $CKD\text{-}EPI_{creatinine}$ observed in young people (before 40 years) because in this equation, the "age" decline factor is applied to the whole age range (whereas the EKFC equation considers the fact that GFR is declining only after 40 years) (8). The evolution of biomarkers considered *per se* (not in equations) could be of interest in such an analysis. A second comment regarding the discrepancies observed between eGFR with cystatin C and creatinine is about the non-GFR determinants of these two biomarkers. These GFR nondeterminants are different for cystatin C (obesity, inflammation, smoking, and thyroid function) and creatinine (diet and muscle mass) (9,10), and relevant for this study, the influence of these determinants could indeed change during aging and thereby affect GFR levels during follow-up. Indeed, one can easily imagine, although it is purely hypothetical, that muscle mass and thus serum creatinine are constantly decreasing with aging, whereas chronic inflammation (and thus, cystatin C) is increasing. However, smoking cessation and weight reduction might also reduce cystatin C levels.

Altogether, these observations (the unhealthy status of the population, the use of equations, and the non-GFR determinants of biomarkers) make a definitive interpretation and generalization of the data from Schaeffner *et al.* (7) quite difficult. Whatever the difficulties in interpreting the results, the article by Schaeffner *et al.* (7) remains illustrative of what can be the evolution of eGFR slopes in a population of old participants. This article raises very interesting questions and opens the door to further research in the field. For sure, future longitudinal data with the measured GFR (iohexol plasma clearance), as those obtained in the Renal Iohexol Clearance Survey (RENIS) study, will be of interest (11). The RENIS study is ongoing. As for all longitudinal studies of this type, we need to be patient.

Disclosures

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Author Contributions

T. Melsom and H. Pottel were responsible for methodology; T. Melsom and H. Pottel provided supervision; P. Delanaye wrote the original draft; and P. Delanaye, T. Melsom and H. Pottel reviewed and edited the manuscript.

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